IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

GAS-007

Applicant	:	Ronald BARTEN et al.
Title	:	METHOD FOR DETECTING DIFFERENT NUCLEIC ACIDS IN PARALLEL
Serial No.	:	10/534,711
Filed	:	June 23, 2005
Group Art Unit	:	1637
Confirmation No.	:	7086
Examiner	:	MUMMERT, Stepanie Kane

Hon. Commissioner of Patents
P.O. Box 1450, Alexandria, VA 22313

October 1, 2009

RESPONSE UNDER 37 CFR § 1.111

Dear Sir:

This is in full and timely response to the Office Action dated April 3, 2009.

Favorable reexamination and reconsideration are respectfully requested in view of the following remarks.

Claim amendments

In this response, the claims are maintained without amendment.

Rejections under 35 USC §103

The rejections of:

1) claims 1-2, 4-9, 12-19 and 21 under 35 U.S.C. I03(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280);

2) claim 3 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Moretti et al. (Biotechniques, 1998, vol. 25, no. 4, p. 716-722).;

3) claim 10-11 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. as applied to claims 1-2, 4-9, 12-19 and 21 above.;

4) claim 20 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Okimoto et al. (Biotechniques, 1996, vol. 21, no. 1, p. 20, 22, 24, 26);

5) claims 22-26, 28 and 29 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Thorp et al. (WO 00/55366; September 2000);

6) claims 26-27 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. and Thorn et al. as applied to claims 22-26, 28 and 29 above, and further in view of Jenison et al.; and

7) claim 30 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. in view of Heath et al. as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Eberwine et. al. (PNAS, 1992, vol. 89, p. 3010-3014); are respectfully traversed.

In traverse, the Examiner has outlined at page 23 of the office action that the methods described by Wong and Heath are ultimately similar, because both make use of a universal primer sequence for the same reason, namely as a binding site for primer extension.

Although this might *(arguendo)* be true, the question whether two methods are similar still depends very much on the concrete circumstances under which a primer extension is performed. In the present case, the primer extension reaction is the only common feature shared by the methods of Wong and Heath. In Wong, the universal primer sequence is used as a tool for generating fragments of different length which are derived from a target nucleic acid, the sequence of which shall be determined. Here, the use of a universal primer sequence and a corresponding binding site in the cloning vector obviates the synthesis of specific primers for each of the different clones to be sequenced. Heath uses the universal primer sequences to amplify a number of different PCR products obtained after a first round of amplification using specific primers. The specific primers introduce a universal primer sequence into the PCR products which allow amplification of these products in a subsequent step using universal primers.

It is further submitted that apart from the primer extension reaction, the methods of Heath and Wong do not share any other common feature. Indeed, the methods serve different purposes and comprise different method steps. This is also reflected by the differences in the structure of the primers which are used in these methods (see below). Thus, the reference to a primer extension as a common feature is submitted to be insufficient to conclude that these methods are indeed similar.

The Examiner further argues that differences in the two methods of Wong and Heath would not teach away from the fact that both methods share a universal primer site as part of a "tag" sequence. Here, the Examiner has overlooked that the method of Heath does in fact not use a tag sequence within the meaning of the teaching of Wong. Wong uses the tag sequence for the identification of a sequencing fragment (see column 3, lines 43-48). In contrast, the "tag" sequence of Heath is a stretch of 6 nucleotides for DNA sequencing. In other words the "tag" sequence of Heath is actually a binding site for a DNA sequencing primer which is identical in the different PCR products. The "tag" according to Heath is in fact another universal primer site to which a sequencing primer can hybridize. Therefore, the teaching of Heath does not disclose a true unique "tag" sequence for identification purposes as referred to by Wong or the present invention. The argument of the Examiner must fail.

In view of the above, we maintain our position that a skilled person would not combine the teachings of Wong and Heath. As furthermore demonstrated below, such a combination would not even render obvious the claimed subject-matter.

It is further submitted that the use of a second primer as taught by Heath in the method of Wong would not be feasible.

According to the Examiner, the methods of Wong and Heath share several similarities and, consequently, it would have been obvious to incorporate a second primer as taught by Heath into the method described by Wong. In the office action dated October 27, 2008, the Examiner also stated in this respect that the method of Wong could also encompass a PCR reaction (see page 9 of the office action of October 27, 2008, 3rd paragraph).

However, such modification of the method of Wong is not only meaningless from a scientific perspective. It is not even

feasible to incorporate a second primer extension step into the sequencing method of Wong. The method of Wong clearly relies upon a primer extension reaction using a single primer for generating a high number of fragments of the target nucleic acid molecules. The primer extension reaction makes use of the chain termination method of Sanger. This means that the reaction is performed in the presence of a dideoxynucleotide (ddATP, ddGTP, ddCTP or ddTTP). The incorporation of a dideoxynucleotide into the growing DNA strand results in the termination of the extension reaction and provides a nucleic acid fragment terminated at a random nucleotide position. When performing the primer extension reaction with each of the 4 different dideoxynucleotides on the same nucleic acid molecule, one would obtain a mixture of fragments of the nucleic acid molecule which statistically includes fragments terminating at every nucleotide position. These fragments can then be separated and detected based on their size, thereby allowing the determination of the nucleotide sequence of the nucleic acid molecule. This is what the method of Wong aims at.

It is directly evident that the method of Wong is based on the use of a single primer extension reaction, and it is unclear what purpose the use of a second primer extension reaction should serve in the context of the sequencing method of Sanger. After the primer extension reaction as taught by Wong has been completed, the main purpose of the Sanger reaction, i.e. the provision of a mixture of fragments with different length of the nucleic acid molecule to be sequenced is achieved. There is no additional benefit of using a second primer extension reaction as required by the claimed method. This is because the claimed method on the one hand and the method of Wong on the other are based on very different principles and are hardly comparable.

However, even if a skilled person nevertheless decided to modify the teaching of Wong by use of a second primer for carrying out a second primer extension reaction, wherein the products from the first primer extension reaction serve as a template, it is highly questionable whether any reaction product is obtained from this second extension reaction. As outlined above, in the method of Wong the products of the first primer reaction are fragments with different length of the nucleic acid molecule to be sequenced. The majority of these fragments will be too short to allow for hybridization of a second primer which is then extended to synthesize the complementary strand of the fragment (compare for Fig. 2 of the present application). Clearly, the primer extension reaction according to Wong is not designed for yielding nucleic acid molecules that can be used as a template for a second extension reaction. Such second extension reaction would most probably not even be possible from a practical perspective. In order to make a second primer reaction feasible in the method of Wong, the skilled person would have to waive the use of dideoxynucleotides in the first primer extension reaction, so as to provide for a full-length template for a second primer extension reaction. However, omitting the dideoxynucleotides-induced chain termination would completely undermine the method of Wong, because a sequencing of the fragments would no longer be possible.

Therefore, the allegation of the Examiner that it would have been obvious to incorporate the primer of Heath to the method of Wong is unfounded. A combination like this would not result in the method of the present invention. If the Examiner maintains her position, it is respectfully requested that this position be substantiated.

It is additionally submitted that the primer format taught by Wong cannot be used in a method as taught by Heath.

The Examiner also assumes at page 24, line 5 that it would have been *prima facie* obvious to incorporate the primer format taught by Wong into a method of PCR amplification as taught by Heath. This assumption is likewise incorrect. In fact, the primers described by Wong are useless in the PCR method that was disclosed by Heath.

The general structure of the primers of Wong is depicted in Figures 1A and 1B of the patent specification. The primers share a universal sequence at their 3′ end that is referred to as 26 in Fig. 1A and 44 in Fig. 1B, respectively. Additionally, both primer formats share a unique tag sequence that is designated 22 in Fig. 1A and 42 in Fig. 1B, respectively.

When initiating polymerase-mediated primer extension, the primers depicted in Fig. 1A and Fig. 1B are extended in the method taught by Wong via the universal binding sites at their 3′ ends in the direction from 5′ to 3′ using the cloning vector as a template for the extension reaction. According to Wong, the 3′ universal binding site is thus used for binding of the primer molecule to the target sequence (within the cloning vector), and the primer is extended starting from the 3′ end in the 5′ direction. For a skilled person, it is evident that such a primer would simply not be suitable for use in the method of Heath. The method of Heath does not work with a universal primer site in the target sequence. Instead, the 3′ ends of the primers used by Heath are target-specific primers which are based on the specific sequence of the target nucleic acid to be amplified. When using a primer with a 3′ universal sequence in the method of Heath, amplification of the target sequences would clearly fail, because said target sequences

do not provide a binding site for the 3′ end of a primer as taught by Wong.

It is apparent for the skilled person that the use of a primer corresponding to the primers taught by Wong in the method of Heath would not provide any result, because amplification of the target nucleic acid would fail. In light of this, the objection raised by the Examiner cannot be maintained without further substantiation. Again, the Examiner is respectfully requested to provide further details from which the Applicant can derive the basis for the objection.

Conclusion

The basic combination upon which all of the rejections are based is submitted as being insufficient to lead the hypothetical person of ordinary skill to the claimed subject matter. That is to say, in order to establish a *prima facie* case of obviousness, it is necessary to show that the hypothetical person of ordinary skill would, without any knowledge of the claimed subject matter and without any inventive activity, be provided with disclosure of all of the claimed elements and then motivated to arrive at the claimed subject matter given the guidance of the cited references when each is fully considered as statutorily required.

It is submitted that the examiner has failed to meet these requirements for at least the reasons advanced above.

Favorable reconsideration and allowance of this application are courteously solicited.

Three month extension of time is hereby requested. A credit card authorization form in the amount of $1,110.00 is attached herewith for the three month extension of time.

Respectfully submitted,

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